Sex-Specific Risks of Major Cardiovascular and Limb Events in Patients With Symptomatic Peripheral Artery Disease

Sex-specific Differences in Risks of Major Cardiovascular and Limb Events in Symptomatic Peripheral Artery Disease

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Women with peripheral artery disease are at lower risk for cardiovascular events. Understanding sex-specific differences requires investigation.

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Background: Patients with peripheral artery disease (PAD) have a higher risk of major adverse cardiovascular events (MACE) as compared with those without PAD.

Objective: The aim of this post hoc analysis was to evaluate sex-specific differences in MACE and limb events in the EUCLID (Examining Use of tiCagreLor In paD) trial.

Methods: Cox proportional hazards models were used to compare time-to-event outcomes stratified by sex. Covariates were introduced after adjusted model selection.

Results: EUCLID enrolled 13,885 patients with PAD (28% women [n=3888]). PAD severity and medical treatment were comparable between sexes, whereas prior lower extremity revascularization was reported less frequently in women (54.8% vs 57.3%; p=0.006). Women were older (mean ± standard deviation [SD] 67.8±8.9 vs 66.1±8.2 years;p<0.001) and more likely to have diabetes mellitus (p=0.004), hypertension, hyperlipidemia, and chronic kidney disease (all p<0.001). Over a mean follow-up of 30 months, women had a lower risk of MACE (9.5% vs 11.2%; adjusted hazard ratio [aHR] 0.77; 95% confidence interval [CI] 0.68–0.88, p<0.001) and all-cause-mortality (7.6% vs 9.7%; aHR 0.61; 95% CI 0.53–0.71, p<0.001). In contrast, risk for major adverse limb events (2.6% vs 3.0%) and hospitalization for acute limb ischemia (1.6% vs 1.7%) were not different by sex.

Conclusions: While women with PAD are at lower risk for MACE and all-cause mortality, risk for limb events was similar between sexes over a mean follow-up of 30 months. Understanding sex-specific differences as well as dissociation between baseline cardiovascular risk and subsequent cardiovascular events require further investigation.

Key words: cardiovascular event, sex, lower extremity, peripheral artery disease, revascularization, risk factor

Condensed Abstract

Patients with peripheral artery disease (PAD) have a higher risk of major adverse cardiovascular events (MACE) as compared with those without PAD. We evaluate sex-specific differences in MACE and limb events in the EUCLID trial. Cox proportional hazards models were used to compare time-to-event outcomes stratified by sex. Covariates were introduced after adjusted model selection. While women with PAD were at lower risk for MACE and all-cause mortality, risk for limb events was similar between sexes over a mean follow-up of 30 months. Understanding sex-specific differences dissociation between baseline cardiovascular risk and subsequent cardiovascular events require further investigation.

Abbreviations

ABI=ankle-brachial index

ALI=acute limb ischemia

CI=confidence interval

EUCLID=Examining Use of tiCagreLor In paD trial

aHR=adjusted hazard ratio

LER=lower extremity revascularization

MACE=major adverse cardiovascular and cerebrovascular events

MALE=major adverse limb events

PAD=peripheral artery disease

TBI=toe-brachial index

INTRODUCTION

Lower extremity peripheral artery disease (PAD) is an important global health problem progressively affecting millions of people worldwide (1). Population-based trends and studies suggest that women are affected at least as often as men, and a recent meta-analysis confirmed a comparable PAD prevalence for both sexes, defined as an ankle brachial index (ABI) ≤0.90 (2).

Nevertheless, while it is recognized that patients with established PAD have a significantly greater risk of major adverse cardiovascular events (MACE), defined as myocardial infarction (MI), stroke, and cardiovascular death, as compared with patients without PAD (3-7), sex-specific differences have not been well defined (8). Evidence of a PAD-related increase in disability and mortality in women is limited, as the overall number of women included in population-based analyses are comparably low and prone to selection bias (5,9). Women are underrepresented in clinical trials (10), which may be partially related to differences in the nature and timing of clinical manifestations of atherosclerosis in women. Moreover, PAD analyses have focused on lower extremity revascularization (LER) outcomes that predominantly are based on non-randomized cohorts and regional and national databases with conflicting findings in the short- and long-term period (11).

To address the gap in knowledge, this post hoc analysis of the global EUCLID trial (Examining Use of tiCagreLor In paD) compares sex-related differences and cardiovascular events including limb ischemic outcomes in a comtemporary, large cohort of male and female patients with established PAD.

METHODS

Design and results of the EUCLID trial (NCT01732822) have been published previously (12). Briefly, EUCLID was an international, multicenter, double-blind trial that evaluated treatment with ticagrelor 90 mg twice daily or clopidogrel 75 mg daily in 13,885 patients with stable

PAD. Eligible patients were ≥50 years of age with lower extremity PAD. Patients were enrolled who were symptomatic with an abnormal ankle-brachial index (ABI) ≤0.80 at screening (n=6010) or a prior LER more than 30 days before randomization (n=7875). Key exclusion criteria included planned use of dual antiplatelet therapy or use of aspirin, high risk of bleeding, treatment with anticoagulation, poor metabolizer status for CYP2C19, planned revascularization (any territory), or major amputation within 3 months. All patients provided written informed consent and institutional review boards approved the protocol at participating institutions. The overall results of the trial did not support superiority of ticagrelor over clopidogrel for the primary endpoint of a composite of cardiovascular death, MI, or ischemic stroke, including sex-specific subgroup analysis (13).

Sex-specific outcomes

The present post hoc analysis focuses on sex-related disparities in the EUCLID trial with a view on PAD status, cardiovascular risk factor profile, treatment, and cardiovascular outcomes. In EUCLID, data on occurrence of the primary endpoint (MACE, a composite of cardiovascular death, MI, or ischemic stroke), all-cause mortality, hospitalization for acute limb ischemia (ALI), major amputation, subsequent LER procedures, and Thrombolysis in Myocardial Infarction (TIMI) major bleeding events were systematically reported according to the trial design. Major adverse limb events (MALE) were defined as the first occurance of ALI or major amputation. ALI defined as a hospitalization involving a rapid or sudden decrease in limb perfusion and either a new pulse deficit, rest pain, pallor, paresthesia, paralysis or objective confirmation of arterial obstruction. MALE plus postrandomization LER was defined as a three component outcome measure including ALI requiring hospitalization, post-randomization LER without fulfilling the criteria of ALI, and major amputation. Endpoints including MALE were adjudicated by a clinical events classification group whose members were blinded to treatment assignment.

Statistical analysis

All patients in EUCLID (n=13,885) were grouped according to sex. Categorical variables are presented as counts (%) and continuous variables are presented as means, standard deviations (SD), medians, 25th percentiles, 75th percentiles, and the number of participants with non-missing data. The differences in baseline characteristics were analyzed using a 2-sample t-test for continuous variables (age, weight, cholesterol, hemoglobin A1C, estimated glomerular filtration rate [eGFR]), and by a chi-square test (all cell sizes ≥5) or Fisher's exact test (at least 1 cell size <5) for categorical variables. Baseline characteristics were summarized by sex for the full population. A backward elimination model selection procedure provided the basis for selecting the covariates to include in the adjusted analysis of each event type. The starting models considered the following covariates: sex, age, weight, tobacco use, region, number of vascular beds, Rutherford classification, history of various medical conditions (major or minor amputations; stroke, TIA, carotid stenosis, or carotid revascularization; myocardial infarction, coronary artery disease, percutaneous coronary intervention, or coronary artery bypass graft; diabetes; hypertension; hyperlipidemia; prior revascularization; chronic kidney disease), and use of various medications prior to randomization (aspirin; clopidogrel; dual antiplatelet therapy; statins; ACE and/or ARB inhibitors). The covariates considered for model building were consistent with the covariates considered for other post-hoc analyses of the EUCLID trial conducted to date. The criteria for selection in the adjusted model for each outcome was $p<0.05$; sex was retained in the adjusted models, regardless of whether it met the significance threshold of $p<0.05$ or not. Cox proportional hazards models were used to compare the time-to-event outcomes. Data were censored for patients in whom the event in question had not occurred at either the censoring date for the primary analysis or the last trial contact when all components of the endpoint in question were assessed, whichever came first. Estimates of the event rate per 100 patient-years (pt-ys) were calculated for each event type

using the following equation: [(number of persons with event) / (sum of time at risk for event for all persons/360)]*100. Kaplan-Meier estimates of the (unadjusted) cumulative proportion of patients for each event were presented by sex. An analysis was conducted to explore the interaction between age group (<65 years, ≥65 years) and sex for MACE and MALE events. The p-values and 95% confidence intervals (CI) for the HRs are reported; p-values and CIs for the HRs are based on the Wald statistic. The statistical testing was not controlled for multiplicity and therefore all p-values reported should be interpreted as descriptive, nominal statistics. All statistical analyses were performed per CPC Standard Operating Procedures (SOPs) using Statistical Analysis System (SAS) version 9.4 or higher (SAS Institute, Inc., Cary, NC).

RESULTS

Demographic and baseline characteristics

Demographics and baseline characteristics are shown in **Table 1**. A total of 3888 (28%) female patients were enrolled in the EUCLID trial. There were no sex-related differences in PAD severity defined according to the Rutherford classification. However, women had fewer prior LER procedures as compared with men (54.8% vs. 57.3%, p=0.006). Female patients with prior LER were more likely to have prior endovascular revascularization as compared with men (72.0% vs. 65.0%, p<0.001), with less common iliac vessel treatment (30.6% vs. 34.0%) and a higher portion of femoropopliteal artery disease being treated (48.4% vs. 42.8%). In accordance with the anatomical distribution pattern of endovascular treatment, female patients underwent more femoropopliteal bypass above the knee, whereas male patients more often had aorto-bifemoral bypass or femoropopliteal bypass below the knee (**Table 2**). Medication including antiplatelet therapy, statins, angiotensin converting enzyme inhibitors and/or angiotensin-receptor blockers for secondary prevention was not different between female and male patients at baseline. Overall, women were significantly older and

were more likely to have diabetes mellitus, hypertension, hyperlipidemia, and chronic kidney disease than men. In contrast, women were less likely to be current or former smokers, and less frequently had a history of cerebrovascular events/revascularizations, coronary events/revascularizations, or established polyvascular disease.

Event rates and outcome

Over a mean follow-up of 30 months, women had a significant lower risk of MACE (9.5% vs 11.2%; adjusted HR [aHR] 0.77; 95% CI 0.68-0.88, p<0.001) and all-cause-mortality than men (7.6% vs 9.7%; aHR 0.61; 95% CI 0.53-0.71, p<0.001) (**Table 3**). Women also had a lower risk of cardiovascular death (4.3% vs 5.4%; aHR 0.65; 95% CI 0.54-0.78, p<0.001), and MI (4.5% vs 5.1%; aHR 0.79; 95% CI 0.66-0.95, p< 0.014), but the risk of ischemic stroke was not different between sexes (2.0% vs 2.2%). In contrast, there was no significant sex-specific difference in MALE (2.6% vs 3.0%) or post-randomization LER (12.6% vs 12.5%) over the mean follow-up of 30 months (**Table 3**). Kaplan-Meier estimates by sex for MACE, all-cause mortality, MALE, and post-randomization LER are shown in **Figure 1A-D**. A subset of 1738 patients, including 491 women (28.2%), underwent post-randomization LER (**Table S1**). A higher proportion of women had an ALI event occurring after post-randomization LER compared with men (6.7% vs 4.7%, Table S1). However, inclusion of post-randomization LER procedures as a time-dependent covariate had no meaningful impact on the risk of subsequent MACE and MALE events between sexes (**Table S2**).

There was a trend for less bleeding in the female patients (TIMI major bleeding 1.4% vs 1.7%; aHR 0.75; 95% CI 0.55–1.02; p=0.069), though none of the differences in bleeding events (i.e., TIMI major bleeding, intracranial bleeding, fatal bleeding) reached statistical significance (**Table 3**).

Event rates by sex and outcome by age groups

Overall, 5885 (42.4%) patients were <65 years of age with a higher proportion of males as compared with women (44.7% vs. 36.4%). While the HRs for females were lower in subjects < 65 and also lower for those ≥65 there was not statistical interaction by age and thus the risk differences for females was consistently lower across these younger and older age groups (**Table 4**). There was also no statistical interaction by age strata and sex for MALE.

DISCUSSION

This EUCLID post hoc analysis of 13,885 patients with PAD reveals several novel findings regarding sex-specific differences in cardiovascular disease that require further investigation. Women with established lower extremity PAD are at lower risk for MACE and all-cause mortality compared with their male counterparts, whereas their risk for MALE, defined as hospitalization for ALI or major amputation, is similar over a follow-up period of 30 months. Interestingly enough, there seems to be an obvious dissociation between risk factors present and clinical outcome. Although women are older and have a higher prevalence of diabetes mellitus, hypertension, and hyperlipidemia, they have a significant lower rate of MACE compared with men.

Similar to other international PAD cohort studies, the EUCLID study population has a higher proportion of male participants, patients from North America and Europe, and those of white race (10,14,15). Numerous factors as age, socioeconomic status, and racial or ethnic affiliation affect participation in clinical trials. In particular, sex-based disparities are not limited to cardiovascular, but are found in cancer or other clinical trials and continue to be a challenge. Call to action campaigns have made some progress, but contemporary rates of female clinical trial participation continue to be about one third (16,17).

A main strength of this large PAD-specific study population is the comparable severity of PAD and medical cardiovascular secondary prevention therapy between sexes. Moreover,

cardiovascular events were adjudicated by a clinical events classification group and less than 2% of patients were lost to follow-up over a mean of 30 months.

Despite comparable severity of lower extremity PAD, male patients had undergone more prior surgical procedures. This sex-specific difference matches data from the literature. Explanations given are differences in perceived physical distress between sexes and development of cardiovascular disease being delayed by about 10 years in women compared with men (11,18,19). Although the rate of prior LER procedures was higher in men by statistical means the absolute difference (2.5%) is not sufficient to assume that men enrolled in EUCLID have more severe PAD to explain differences on this basis. In contrast to the increased rate of events and polyvascular disease manifestation in men in EUCLID, the prevalence of cardiovascular risk factors is more pronounced in women. Moreover, in accordance with data from the REACH registry, women are significantly older (20). The sex-specific dissociation of risk factors with MALE in a homogeneous PAD population suggests other genetic factors that either act independently or interact with the mode of action of the risk factor. Evidence on sex-specific cardiovascular event rates in PAD populations is poor or based on out-of-date data surveys (10). Sigvant et al. analyzed studies with at least 1 year of follow-up and found no risk difference by sex for cardiovascular mortality, but an increased risk for all-cause mortality by one-third in male patients with PAD (21). This is in accordance with a propensity score matched analysis of inpatients in Germany that identified male patients with PAD to be at risk for mortality during 4 years of follow-up (18). On the other hand and in contrast, 2 PAD cohort studies from Canada and the Netherlands found no sex difference for mortality (22,23). Based on conflicting results on outcomes by sex, a call to action review article by the Americican Heart Association was published underlining the need for more robust data and resulting consequences (8).

It is generally accepted, and shown for the EUCLID population as well, that presence of polyvascular disease, when compared with patients with PAD alone, is associated with an

increased risk for MACE (24). Therefore, the more advanced manifestation of atherosclerosis in several arterial beds in men must be considered as a reason for sex-differences in MACE shown in this analysis. The reason for the more advanced disease in men with comparable severity of PAD, however, remains to be elucidated. In contrast to MACE, limb events are comparable between sexes in EUCLID over the follow-up period of 30 months. In a small subgroup of patients with post-randomization LER, the only difference is a slight increase in ALI in female patients. Egorova et al. compared inpatient data by sex that showed constantly higher rates of emergency PAD hospitalization in women over 10 years (25). Data from a US registry indicated a more frequent rate of LER for rest pain in women when compared with men (19). Factors discussed as reasons for a higher risk for ALI by sex consider that women were older when undergoing LER, they have more advanced disease, smaller arteries, and several differences regarding epidemiology and clinical presentation including awareness of PAD (8).

Sex-specific differences between risk of MACE and prevalence of classical cardiovascular risk factors are described for non-PAD populations, but results are conflicting as populations studied vary. The historical Finnmark study showed that in women more than in men smoking was a stronger risk factor for MI during 12 years of follow-up (26). Further epidemiological data from a general population pointed to an increased risk for women over men with regard to cardiovascular mortality and MI by smoking and diabetes (27,28). Two meta-analyses, each including more than 750,000 individuals, reported on a pronounced relative risk by female sex for fatal coronary heart disease and stroke in patients with diabetes mellitus (29,30). In contrast to classical cardiovascular risk factors, it is believed that estrogen has a protective effect on the vascular system and hormone receptor signalling may play a leading role for better understanding risk differences in the pathogenesis of atherosclerotic arterial disease influenced by age (31). The fact that its protective impact gets lost with menopause, and thereafter prevalence of vascular disease increases for women, underlines the robustness

of our data of a reduced risk difference by sex and older age group for MACE (32-35). Nevertheless and in contrast, the Heart and Estrogen/progestin Replacement Study did not demonstrate a benefical effect of estrogen/progestin replacement to reduce risk of cardiovascular events in postmenopausal women with coronary heart disease (36).

Limitations

The EUCLID trial was not designed to specifically evaluate sex-related differences in the baseline characteristics or outcomes in PAD patients. Potential confounders in this post hoc analysis might include a selection bias for patients from high income countries and racial and ethnic differences (1,8,14,37-39). Black women, reported to have a disproportional high risk of cardiovascular events and poor limb specific outcome, were underrepresented and sex-specific disparities might have additional racial causes (40). Recently relations between ethnicity, socioeconomic status, gender and outcomes in PAD patients have been described (41). EUCLID enrolled African American patients and patients from low income countries, however, numbers were small and selection bias likely. Nevertheless, an influence by ethnicity on sex-specific differences found in the EUCLID post hoc analysis cannot be excluded (41). Disparities in cardiovascular risk factors were limited to prevalence without information on the cumulative effect as smoking pack years, duration of diabetes, or control of arterial hypertension. Since groups were not matched for each of the modifiable risk factors, conclusions made must be taken with caution. It can not be excluded that PAD was more severe in male patients, although disease severity was comparable, because more men than women had a prior LER before study entry. Morteover, prior LER was shown to be an independent risk factor for subsequent MI and ALI and both events independently increased mortality risk in EUCLID (42). Finally, the proportion of men with a history of surgical revascularization of any kind was higher before study entry, which might also suggest a more severe burden of atherosclerosis in men that influenced MACE during follow-up (43).

Conclusions

Female patients with PAD have a significantly reduced risk for MACE and all-cause mortality compared with men, while risk for MALE is similar for both sexes over a mean follow-up of 30 months. Sex-related differences are not explained by cardiovascular risk factor prevalence and medical interventions alone. Further investigation in defining additional factors responsible for sex-related disparities in outcomes of patients with PAD is needed.

Clinical Perspectives

- **Competency in medical knowledge:** Risk for Major Adverse Cardiovascular Events is higher for male than for female patients with symptomatic PAD. Equality in inclusion of both sexes in cardiovascular trials is an unmet need to improve recognition of sex-specific differences.
- **Translational outlook:** Sex must be considered as a crucial factor for influencing the translation of basic research to clinical trials testing new therapies to inform clinical practice in cardiovascular medicine .

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Figure Legends

Figure 1 (Central Figure). Kaplan-Meier curves for (A) major adverse cardiovascular events, (B) all-cause mortality, (C) major adverse limb events, and (D) post-randomization LER in female and male patients.

Footnote: HR (95% CI) and p-values for the time from randomization to the first occurrence of the event is from a Cox proportional hazards model with a factor for sex (unadjusted analysis) and from a Cox proportional hazards model including baseline factors (adjusted analysis).

Table 1. Demographic and baseline characteristics by sex

Characteristic	Male (N=9997)	Female (N=3888)	p-value*	Total Population (N=13,885)
Age, yrs			<0.001	
median (25th, 75th)	66.0 (60.0, 72.0)	66.0 (60.0, 72.0)		66.0 (60.0, 73.0)
mean (±SD)	66.1 (8.2)	67.8 (8.9)		66.6 (8.4)
Race, no. (%)			<0.001	
White	8176 (81.8)	3134 (80.6)		11,310 (81.5)
Black or African American	293 (2.9)	276 (7.1)		569 (4.1)
Asian	1294 (12.9)	340 (8.7)		1634 (11.8)
Native Hawaiian or Pacific Islander	5 (<0.1)	0		5 (<0.1)
American Indian or Alaska Native	65 (0.7)	60 (1.5)		125 (0.9)
Other	164 (1.6)	78 (2.0)		242 (1.7)
Weight, kg	79.9 (69.9, 90.0)	69.9 (60.0, 80.0)	<0.001	76.5 (66.0, 88.0)
Region			<0.001	
North America	1979 (19.8)	1066 (27.4)		3045 (21.9)
Europe	5670 (56.7)	1828 (47.0)		7498 (54.0)
Asia	1272 (12.7)	330 (8.5)		1602 (11.5)
Central/South America	1076 (10.8)	664 (17.1)		1740 (12.5)
Inclusion criteria			0.004	
Prior LER	5746 (57.5)	2129 (54.8)		7875 (56.7)
ABI/TBI criteria	4251 (42.5)	1759 (45.2)		6010 (43.3)
Rutherford classification for index limb at study entry			0.946	
Asymptomatic	1878 (18.8)	723 (18.6)		2601 (18.7)
Mild/moderate claudication	5310 (53.1)	2100 (54.0)		7410 (53.4)
Severe claudication	2335 (23.4)	893 (23.0)		3228 (23.3)
Critical limb ischemia				
Rest pain	276 (2.8)	102 (2.6)		378 (2.7)

Characteristic	Male (N=9997)	Female (N=3888)	p-value*	Total Population (N=13,885)
Minor tissue loss	152 (1.5)	55 (1.4)		207 (1.5)
Major tissue loss	43 (0.4)	15 (0.4)		58 (0.4)
Any prior amputation	746 (7.5)	220 (5.7)	<0.001	966 (7.0)
Prior major amputation above ankle (either limb)	261 (2.6)	78 (2.0)	0.038	339 (2.4)
History of only minor amputation	485 (4.9)	142 (3.7)	0.002	627 (4.5)
Tobacco use			<0.001	
Never smoked	1497 (15.0)	1487 (38.7)		2984 (21.6)
Current smoker	3284 (33.0)	1005 (26.1)		4289 (31.1)
Former smoker	5176 (52.0)	1354 (35.2)		6530 (47.3)
Medical history†				
Stroke, TIA, carotid stenosis, or carotid revascularization	4120 (41.2)	1388 (35.7)	<0.001	5508 (39.7)
MI, CAD, PCI, or CABG	3129 (31.3)	903 (23.2)	<0.001	4032 (29.0)
Diabetes mellitus	3774 (37.8)	1571 (40.4)	0.004	5345 (38.5)
Hypertension	7705 (77.1)	3152 (81.1)	<0.001	10,857 (78.2)
Hyperlipidemia	7437 (74.4)	3043 (78.3)	<0.001	10,480 (75.5)
CKD‡	2040 (21.1)	1292 (34.1)	<0.001	3332 (24.7)
Number of vascular beds			<0.001	
1	5440 (54.4)	2364 (60.8)		7804 (56.2)
2	3479 (34.8)	1209 (31.1)		4688 (33.8)
3	1078 (10.8)	315 (8.1)		1393 (10.0)
Medications taken up to 30 days prior to randomization†				
Aspirin	6675 (66.8)	2596 (66.8)	>0.999	9271 (66.8)
Clopidogrel	3232 (32.3)	1241 (31.9)	0.642	4473 (32.2)
DAPT	1609 (16.1)	658 (16.9)	0.235	2267 (16.3)
Statins	7307 (73.1)	2874 (73.9)	0.322	10,181 (73.3)

Characteristic	Male (N=9997)	Female (N=3888)	p-value*	Total Population (N=13,885)
ACE inhibitor and/or ARB	6337 (63.4)	2472 (63.6)	0.834	8809 (63.4)
Laboratory parameters at baseline, median (25th, 75th)				
LDL-C, mmol/L	2.50 (1.90, 3.20)	2.60 (2.00, 3.40)	<0.001	2.50 (1.90, 3.20)
HDL-C, mmol/L	1.10 (1.00, 1.40)	1.30 (1.10, 1.60)	<0.001	1.20 (1.00, 1.40)
Total cholesterol, mmol/L	4.40 (3.70, 5.20)	4.70 (4.00, 5.60)	<0.001	4.50 (3.80, 5.30)
Hemoglobin A1C, %	6.40 (5.80, 7.50)	6.60 (5.90, 7.90)	0.583	6.40 (5.80, 7.60)
eGFR, mL/min/1.73m^2	77.6 (63.1, 92.9)	69.1 (54.3, 83.9)	<0.001	75.0 (60.2, 90.6)

Values are no. (%), unless otherwise indicated.
*P-values for continuous variables are based on 2-sample t-tests; p-values for categorical variables are based on a chi-square tests (all cell sizes ≥5) or Fisher's exact tests (at least one cell size <5).
†Percentages for medical history and medications taken up to 30 days prior to randomization may add up to a value greater than 100%.
‡Participants with a calculated eGFR<60 mL/min/1.73m^2.
ABI=ankle-brachial index; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; CABG=coronary artery bypass grafting; CAD, coronary artery disease; CKD=chronic kidney disease; DAPT=dual antiplatelet therapy; eGFR=estimated glomerular filtration rate; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; LER=lower extremity revascularization; MI=myocardial infarction; PCI=percutaneous coronary intervention; SD=standard deviation; TBI=toe-brachial index; TIA=transient ischemic attack.

Table 2. Baseline limb characteristics of patients with prior revascularization by sex

Characteristic	Male (N=5732)	Female (N=2129)	p-value*
Type of most recent revascularization procedure prior to randomization†			
Endovascular	3725 (65.0)	1532 (72.0)	<0.001
Surgical	2280 (39.8)	679 (31.9)	<0.001
Time since most recent revascularization procedure prior to randomization	5,732	2,129	
>30 days to ≤6 months (180 days)	1854 (32.3)	679 (31.9)	0.703
>6 months (180 days) to ≤2 years (720 days)	1783 (31.1)	697 (32.7)	0.166
>2 years (720 days)	2095 (36.5)	753 (35.4)	0.333
Location of most recent prior endovascular revascularization prior to randomization‡			
Iliac	1266 (34.0)	469 (30.6)	0.004
Common femoral artery	156 (4.2)	73 (4.8)	0.428
Superficial femoral artery	1385 (37.2)	620 (40.5)	0.076
Popliteal	208 (5.6)	121 (7.9)	0.003
Tibial	323 (8.7)	117 (7.6)	0.153
Type of most recent prior surgical revascularization prior to randomization§			
Endarterectomy (CFA/SFA)	385 (16.9)	113 (16.6)	0.576
Aorta-bifemoral bypass	420 (18.4)	100 (14.7)	0.107
Axillary-femoral bypass	48 (2.1)	13 (1.9)	0.928
Femoropopliteal bypass (above knee)	499 (21.9)	164 (24.2)	0.028
Femoropopliteal bypass (below knee)	375 (16.4)	91 (13.4)	0.185
Other	4 (0.2)	1 (0.1)	>0.999

Characteristic	Male (N=5732)	Female (N=2129)	p-value*
Rutherford classification for index limb upon study entry			
Asymptomatic	1778 (31.0)	682 (32.0)	0.391
Mild/moderate claudication	2666 (46.5)	993 (46.6)	0.923
Severe claudication	1033 (18.0)	365 (17.1)	0.364
Critical limb ischemia			
Rest pain	154 (2.7)	47 (2.2)	0.231
Minor tissue loss	81 (14)	33 (1.6)	0.653
Major tissue loss	19 (0.3)	9 (0.4)	0.546
Previous amputation‖	474	145	
Above knee	103 (21.7)	34 (23.4)	0.663
Below knee	356 (75.1)	109 (75.2)	0.987
Ankle disarticulation	6 (1.3)	1 (0.7)	>0.999
Transtibial	69 (14.6)	20 (13.8)	0.819
Partial foot	39 (8.2)	18 (12.4)	0.127
Toe	254 (53.6)	76 (52.4)	0.804

Values are no. (%).
*P-values are based on a chi-square tests (all cell sizes ≥5) or Fisher's exact tests (at least one cell size <5).
†Most recent prior revascularization procedure is defined as the procedure which occurred closest to the date of randomization. Participants with both a surgical and endovascular procedure on the same closest date will be counted once for each procedure.
‡Percentages are based on the number of patients whose most recent prior revascularization procedure was endovascular. Patients who report the same location in both limbs are counted only once for that location. Patients may report multiple locations for the procedure.
§Percentages are based on the number of patients whose most recent prior revascularization procedure was surgical. Patients who report the same type in both limbs are counted only once for that type. Patients may report multiple types for the procedure.
‖Patients reporting multiple amputations prior to study entry are counted at most once for each amputation location.
CFA=combined femoral artery; SFA=superficial femoral artery.

Table 3. Event rates and hazard ratios (females vs. males) for each outcome

	Male (N=9997)		Female (N=3888)		Unadjusted		Adjusted	
	No. (%)	Event Rate/ 100 Pt-Yrs	No. (%)	Event Rate/ 100 Pt-Yrs	HR (95% CI)	p-value	HR (95% CI)	p-value
MACE	1123 (11.2)	4.63	368 (9.5)	3.87	0.84 (0.74, 0.94)	0.003	0.77 (0.68, 0.88)	<0.001
CV death	539 (5.4)	2.14	167 (4.3)	1.70	0.80 (0.67, 0.95)	0.010	0.65 (0.54, 0.78)	<0.001
MI	508 (5.1)	2.08	175 (4.5)	1.83	0.88 (0.74, 1.04)	0.149	0.79 (0.66, 0.95)	0.014
Ischemic stroke	223 (2.2)	0.90	77 (2.0)	0.80	0.88 (0.68, 1.14)	0.346	0.88 (0.67, 1.16)	0.351
All-cause mortality	966 (9.7)	3.80	297 (7.6)	3.00	0.79 (0.69, 0.90)	<0.001	0.61 (0.53, 0.71)	<0.001
MALE	296 (3.0)	1.20	103 (2.6)	1.07	0.89 (0.71, 1.12)	0.313	0.90 (0.71, 1.14)	0.369
MALE plus post-randomization LER	1.362 (13.6)	5.91	522 (13.4)	5.81	0.99 (0.89, 1.09)	0.776	0.99 (0.88, 1.11)	0.839
ALI requiring hospitalization	170 (1.7)	0.69	62 (1.6)	0.64	0.94 (0.70, 1.25)	0.652	0.90 (0.66, 1.24)	0.536
Major amputation	162 (1.6)	0.65	54 (1.4)	0.56	0.85 (0.63, 1.16)	0.312	0.81 (0.58, 1.12)	0.198
Post-randomization LER	1.247 (12.5)	5.37	491 (12.6)	5.44	1.01 (0.91, 1.13)	0.784	1.02 (0.90, 1.14)	0.797
TIMI major bleeding	169 (1.7)	0.78	53 (1.4)	0.65	0.83 (0.61, 1.13)	0.242	0.75 (0.55, 1.02)	0.069
Intracranial bleeding	53 (0.5)	0.24	15 (0.4)	0.18	0.75 (0.42, 1.33)	0.329	0.72 (0.40, 1.28)	0.266
Fatal bleeding	23 (0.2)	0.11	7 (0.2)	0.09	0.81 (0.35, 1.89)	0.625	0.84 (0.36, 1.95)	0.683

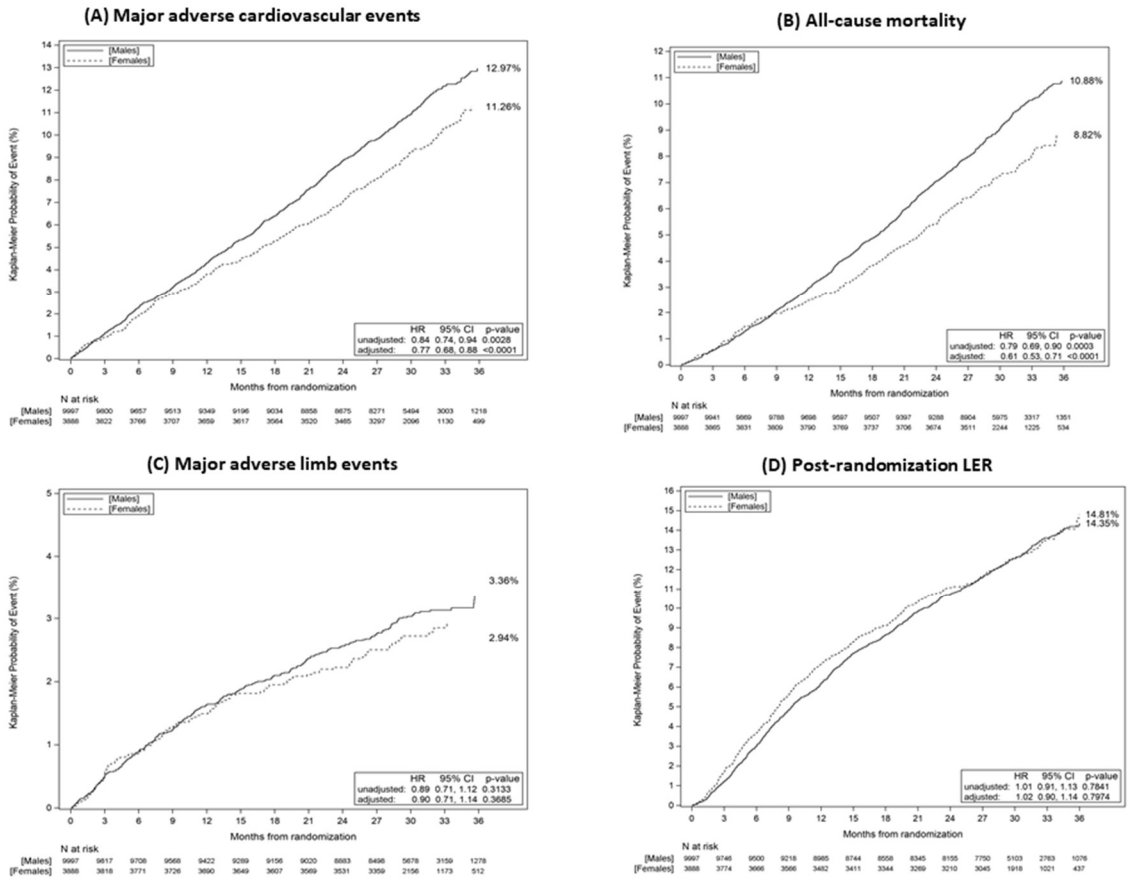
No. (%) represents the raw number and percent of patients reporting at least 1 event.
Event rate/100 patient-years is calculated as [(number of patients with event) / (sum of time at risk for event for all patients/360)]*100.
The p-values and 95% CIs presented in this table have not been adjusted for multiplicity, and therefore inferences drawn from these p-values and 95% CIs may not be reproducible.
ALI=acute limb ischemia; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; LER=lower extremity revascularization; MACE=major adverse cardiovascular events; MALE=major adverse limb events; MI=myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction.

Table 4. Event rates and hazard ratios by sex and age group

	Age Group (Yrs)	Male (N=9997)		Female (N=3888)		Adjusted HR (95% CI)	p-value	Interaction p-value
		n/Nsub (%)	Event Rate/ 100 Pt-Yrs	n/Nsub (%)	Event Rate/ 100 Pt-Yrs			
MACE	<65	403/4471 (9.0)	3.65	85/1414 (6.0)	2.40	0.60 (0.47, 0.77)	<0.001	
	≥65	720/5526 (13.0)	5.45	283/2474 (11.4)	4.74	0.76 (0.65, 0.89)	<0.001	0.111
MALE	<65	145/4471 (3.2)	1.30	36/1414 (2.5)	1.01	0.86 (0.59, 1.25)	0.043	
	≥65	151/5526 (2.7)	1.12	67/2474 (2.7)	1.10	0.93 (0.69, 1.26)	0.648	0.741

Nsub=the number of patients in the given subgroup for that treatment group.
Event rate/100 patient-years is calculated as [(number of patients with event) / (sum of time at risk for event for all patients/360)]*100.
Time from randomization to the first occurrence of the event is compared between sex groups using an adjusted Cox proportional hazards model which contains factors for: Major Adverse Cardiovascular Event (MACE): sex, age group, an interaction term for sex*age group, baseline weight, tobacco use at baseline, region, number of prior vascular beds, Rutherford classification at baseline, history of any major amputations, history of only minor amputations, history of stroke, TIA, carotid stenosis, or carotid revascularization, history of diabetes, CKD at baseline (calculated eGFR <60 ml/min/1.73m 2), statin use up to 30 days prior to randomization, and Clopidogrel use up to 30 days prior to randomization, and for Major Adverse Limb Event (MALE):sex, age group, an interaction term for sex*age group, prior revascularization, baseline weight, Rutherford classification at baseline, history of any major amputations, history of only minor amputations, history of diabetes, statin use up to 30 days prior to randomization, and DAPT use up to 30 days prior to randomization.
CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MALE=major adverse limb event.

Figure 1.


(A) Major adverse cardiovascular events
[Males]
[Females]
12.97%
11.26%
Kaplan-Meier Probability of Event (%)
HR 95% CI p-value
unadjusted: 0.84 0.74, 0.94 0.0028
adjusted: 0.77 0.68, 0.88 <0.0001
Months from randomization
N at risk
[Males] 9997 9800 9657 9513 9349 9196 9034 8858 8675 8271 5494 3003 1218
[Females] 3888 3822 3766 3707 3659 3617 3564 3520 3465 3297 2096 1130 499
(B) All-cause mortality
[Males]
[Females]
10.88%
8.82%
Kaplan-Meier Probability of Event (%)
HR 95% CI p-value
unadjusted: 0.79 0.69, 0.90 0.0003
adjusted: 0.61 0.53, 0.71 <0.0001
Months from randomization
N at risk
[Males] 9997 9941 9869 9788 9698 9597 9507 9397 9288 8904 5975 3317 1351
[Females] 3888 3865 3831 3809 3790 3769 3737 3706 3674 3511 2244 1225 534
(C) Major adverse limb events
[Males]
[Females]
3.36%
2.94%
Kaplan-Meier Probability of Event (%)
HR 95% CI p-value
unadjusted: 0.89 0.71, 1.12 0.3133
adjusted: 0.90 0.71, 1.14 0.3685
Months from randomization
N at risk
[Males] 9997 9817 9708 9568 9422 9299 9156 9020 8883 8496 5678 3159 1278
[Females] 3888 3818 3771 3726 3690 3649 3607 3569 3531 3359 2156 1173 512
(D) Post-randomization LER
[Males]
[Females]
14.81%
14.35%
Kaplan-Meier Probability of Event (%)
HR 95% CI p-value
unadjusted: 1.01 0.91, 1.13 0.7841
adjusted: 1.02 0.90, 1.14 0.7974
Months from randomization
N at risk
[Males] 9997 9746 9500 9218 8965 8744 8558 8345 8155 7750 5103 2763 1076
[Females] 3888 3774 3666 3566 3482 3411 3344 3269 3210 3045 1918 1021 437